REMARKS

In the present amendment, claims 6, 9 and 10 have been amended. Claim 8 has been canceled. The amendment to claim 6 is supported on page 9, lines 3-5 and in Example 3. Claims 9 and 10 have been amended to correct the way the claims are phrased. Support for the amendments to claims 9 and 10 can be found throughout the specification. No new matter is believed to be added.

After entry of these amendments, claims 1-3, 5-7, 9-15, 17-27 and 29-39 are pending.

Rejection of claims under 35 U.S.C. § 112, second paragraph

Claims 6, 7-10 and 27 remain rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite.

Specifically, the Examiner alleges that the phrase "any part of the cavity" in claim 6 renders the claims indefinite. Claims 7-10 and 27 are included in this rejection because these claims are dependent on rejected claim 6 and do not cure its deficiencies. Applicants have amended claim 6 to remove this phrase so that it reads "said GR Site II." By this amendment, Applicants believe that they have obviated this rejection.

Rejection of claims under 35 U.S.C. § 102(e) and § 103(a)

Claims 1, 5-10, 16, 27 and 29 remain rejected under 35 U.S.C. § 102(e) and § 103(a) as allegedly being anticipated by or, in the alternative, as obvious over US patent 6,965,850 (hereinafter "'850"). Specifically, the Examiner alleges that Applicants have not provided any evidence, for example a picture of the three-dimensional structure of GR, that the Site II in the instant application differs from the binding site in '850 other than the argument that the amino acid residues are different.

Applicants respectfully traverse this rejection and submit that '850 does not teach each and every element of the claims. Claims 1, 5, 6 and 29 are directed to methods for evaluating the potential of a chemical entity to bind to a GR Site II, methods of designing a ligand of a GR Site II, methods for identifying modulators of a GR, and methods of identifying a ligand of a GR Site II, respectively. Claims 1, 5, 6 and 29 also recite that the GR Site II is comprises the amino acids E537-V543, L566, G567, Q570-W577, S599-A607, W610, R611, R614, Q615, P625, Y663, L664 and K667 and is defined by the structure coordinates according to Table 1. Claim 1 also

recites the structure coordinates according to Tables, III-V. Amended claim 6 also recites that the modulator of GR Site II induces transrepression.

Applicants were the first to identify Site II NHRs as a binding site whose ligands modulate NHRs. Applicants were also the first to identify that Site II is a binding site which is distinct from the coactivator site that is disclosed in '850. The coactivator site, as defined in Fig. 19 of '850, shares a common wall with Site II of the instant application although each site has a unique binding cavity and is located on opposite sides of GR. Per the Examiner's suggestion, Applicants have enclosed herein a picture of the three-dimensional structure of GR and its binding sites ("Exhibit A") as evidence that these sites are different. The coactivator site of '850 is shown as the light blue surface (left), while Site II is shown as the magenta surface (right). The two sites share several residues in common (shown in green, mostly on H3). The common residues are comprised of amino acids 571, 572, 574 and 575, all on H3 and amino acid 600 located on H4. In addition, Tif2 is represented in this picture in light purple as it is known to bind specifically the coactivator site of GR. This three-dimensional picture clearly shows that the coactivator site of '850 and Site II of the instant invention are distinct binding sites that, while they share common residues, are located on opposite sides of GR and have distinct binding partners. Additionally, claim 6 is currently amended to recite the phrase "wherein said modulator of said GR induces transrepression." Example 3 of the instant specification demonstrates that the binding of chemical entities to Site II results in transrepression by inhibiting AP-1 transcriptional activity. The coactivator site of '850 does not induce transrepression upon binding but rather enhances transcription upon binding. This evidence provides additional support that the coactivator site of '850 and Site II of the instant application are separate and distinct binding sites on GR.

Therefore, as outlined above, the site in '850 corresponds to the coactivator site of GR which is distinct from Site II of the instant application and, as such, '850 does not anticipate the instant invention as it does not disclose each and every element of the claims. Applicants respectfully request reconsideration by the Examiner and withdrawal of this rejection.

Claims 1, 5-10, 16, 27 and 29 also stand rejected under §103(a) as being unpatentable over '850. As discussed above, Applicant submits that '850 neither discloses the subject matter of the claims 1, 5 and amended claim 6 nor claims 7, 9-10, 27 and 29 that ultimately depend therefrom. Accordingly, Applicants request reconsideration and withdrawal of this rejection.

The Examiner has also rejected claims 1, 5-10, 16, 27 and 29 under 35 U.S.C. § 103(a) as being unpatentable over WO 00/52050 (hereinafter "'050") in view of US Patent 5,856,116 (hereinafter "'116").

Claims 1 and 5 are directed to methods for evaluating the potential of a chemical entity to bind to GR Site II, wherein said GR Site II is a structure described by the structure coordinates of amino acids E537-V543, L566, G567, Q570-W577, S599-A607, W610, R611, R614, Q615, P625, Y663, L664 and K667 of SEQ ID NO:1 according to Table I, Table III, Table IV or Table V. Amended claim 6 further specifies that the modulator to GR Site II induces transrepression. The Examiner alleges that '050 provides one of ordinary skill in the art with motivation to identify potential inhibitors for GR as they teach the agonist and antagonist can be used for the treatment of various known human diseases such as inflammation and disease. While '050 discloses the use of GR homology models to design new GR ligands, '050 would not make it obvious that one of ordinary skill in the art should or could utilize Site II to design such ligands. Additionally, '050 utilized the estrogen receptor (hereinafter "ER") as the homology model for GR although there is only 26% homology between ER and GR. Further, '050 states that a homology model "can never be correct in all details, but it should capture one or more of the essential characteristics of the protein" (page 4, lines 11-12) thereby diminishing the reliability of this homology model and making it less applicable to alternative GR binding sites. Therefore, because '050 does not disclose Site II as a possible binding site for GR or as being useful in designing ligands and/or modulators based upon this site, and the fact that there is only 26% homology between ER and GR, it would not have been obvious for one of ordinary skill in the art to utilize Site II of the instant application to design ligands and modulators of GR, in particular those that induce transrepression.

Applicants respectfully submit that '116 does not cure the deficiencies of '050, and that accordingly the combination of '050 and '116 does not suggest Applicants' claimed invention. Accordingly, Applicants request reconsideration and withdrawal of this rejection.

The Examiner has also rejected claims 1, 5-10, 16, 27 and 29 under 35 U.S.C. § 103(a) as being unpatentable over US Patent Application Publication No. 2005/0181362 (hereinafter "'362"). Specifically, the Examiner alleges that '362 teaches the crystallization of the complex of GR ligand binding with two ligands and the determination of the three-dimensional structure by the X-ray diffraction method.

Claims 1, 5 and amended claim 6 are directed to methods for evaluating the potential of a chemical entity to bind to GR Site II, wherein said GR Site II is a structure described by the structure coordinates of amino acids E537-V543, L566, G567, Q570-W577, S599-A607, W610, R611, R614, Q615, P625, Y663, L664 and K667 of SEQ ID NO:1 according to Table I, Table III, Table IV or Table V. Amended claim 6 also recites that the modulator to GR Site II induces transrepression. '362 does not teach the methods of the instant invention as '362 does not disclose Site II as a binding site for GR. As described in the '362 specification and shown in Fig. 7, '362 utilizes the GR ligand binding site that binds dexamethasone to generate its crystal. Fig. 3 of the instant application clearly shows that dexamethasone binds Site I of GR and not Site II. Therefore, one of ordinary skill in the art would not be motivated to identify potential ligands and/or modulators of Site II of GR based upon the disclosure of '362.

As such, Applicants submit that '362 does not disclose the subject matter of the claims 1, 5 and amended claim 6 nor claims 7-10, 27 and 29 that ultimately depend therefrom and, therefore, do not render these claim obvious. Accordingly, Applicants request reconsideration and withdrawal of this rejection.

Rejection of claims 1, 5-10, 16, 27 and 29 under 35 U.S.C. § 103(a) over '362 in view of '850

The Examiner has rejected claims 1, 5-10, 16, 27 and 29 under 35 U.S.C. § 103(a) as being unpatentable over '362 in view of '850. For the foregoing reasons, '362 neither discloses the subject matter of the claims 1, 5 and amended claim 6 nor claims 7-10, 27 and 29 that ultimately depend therefrom and, therefore, do not render these claim obvious. Applicants respectfully submit that '850 does not cure the deficiencies of '362, and that accordingly the combination of '362 and '850 does not suggest Applicants' claimed invention. Applicants request reconsideration and withdrawal of this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, allowance of the application is respectfully requested. The Examiner is invited to contact the undersigned if there are any questions concerning the prosecution of this application.

The Commissioner is authorized to charge Deposit Account 19-3880 (Bristol-Myers Squibb Company) for any requisite fees due or to credit any overpayment.

Respectfully submitted,

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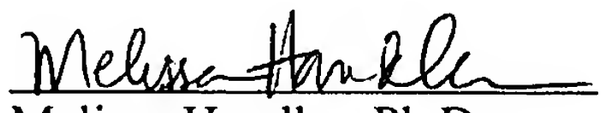

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Date: November 19, 2007

Encl: Exhibit A

Exhibit A